UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/700,816	11/04/2003	Zuoshang Xu	UMY-038	9864

959 7590 08/11/2008

LAHIVE & COCKFIELD, LLP
FLOOR 30, SUITE 3000
ONE POST OFFICE SQUARE
BOSTON, MA 02109

EXAMINER	
MCGARRY, SEAN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
08/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/700,816	XU ET AL.	
	Examiner	Art Unit	
	Sean R. McGarry	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-12 and 28-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12 and 28-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 7/11/08, with respect to the rejections of claims 1-12 and 28-48 under 35 U.S.C. 103(a) as being unpatentable over Kreutzer et al [US 2005/0074757 A1] as the primary reference have been fully considered and are persuasive. Therefore, the rejections have been withdrawn. However, upon further consideration, a new ground(s) of rejection is made in view of Tuschl et al [US 20042059247 A1] in combination with the references of record.

In view of the above the finality of the previous Official Action has been withdrawn.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-12 and 28-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al [US 20042059247 A1], Elbashir [The EMBO Journal Vol. 20(23), 2001, cited by applicant as C15 in IDS filed 9/17/07], Klug et al [European Journal of Physiology, Vol. 441 (6 Suppl): R205, 2001], Brown et al [WO 94/19493], Siddique et al [Neurology Vol. 47(suppl 2): S27-S35, 1996], and Kunst et al [Nature Genetics Vol. 15: 91-94, 01/15/96].

The instant invention is drawn to the inhibition of a targeted specified allele in a cell via siRNA. The invention is more specifically drawn to dominant gain of function alleles of specified diseases and to specified alleles and to the use of specific siRNA and shRNA targeted to specific ALS alleles. The invention is clearly set forth in the claims and no interpretation is required to apply the prior art.

Tuschl et al have taught the use of siRNA compound for mediating target-specific RNA interference where the siRNA agents have improved efficacy and safety compared to prior art agents. Tuschl et al have taught: [0030] The target gene to which the RNA molecule of the invention is directed may be associated with a pathological condition. For example, the gene may be a pathogen-associated gene, e.g. a viral gene, a tumor-associated gene or an autoimmune disease-associated gene. The target gene may also be a heterologous gene expressed in a recombinant cell or a genetically altered organism. By determinating or modulating, particularly, inhibiting the function of such a gene valuable information and therapeutic benefits in the agricultural field or in the medicine or veterinary medicine field may be obtained.; [0175] In order to examine the sequence-specificity of target recognition, we introduced sequence changes into the paired segments of siRNA duplexes and determined the efficiency of silencing. Sequence changes were introduced by inverting short segments of 3- or 4-nt length or as point mutations (FIG. 18). The sequence changes in one siRNA strand were compensated in the complementary siRNA strand to avoid perturbing the base-paired siRNA duplex structure. The sequence of all 2-nt 3' overhangs was TT (T, 2'-deoxythymidine) to reduce costs of synthesis. The TT/TT reference siRNA duplex was

comparable in RNAi to the wild-type siRNA duplex AA/UG (FIG. 17). The ability to mediate reporter mRNA destruction was quantified using the translation-based luminescence assay. Duplexes of siRNAs with inverted sequence segments showed dramatically reduced ability for targeting the firefly luciferase reporter (FIG. 18). The sequence changes located between the 3' end and the middle of the antisense siRNA completely abolished target RNA recognition, but mutations near the 5' end of the antisense siRNA exhibit a small degree of silencing. Transversion of the A/U base pair located directly opposite of the predicted target RNA cleavage site, or one nucleotide further away from the predicted site, prevented target RNA cleavage, therefore indicating that single mutation within the centre of a siRNA duplex discriminate between mismatched targets.; [0180] Target recognition is a highly sequence-specific process, mediated by the siRNA complementary to the target. The 3'-most nucleotide of the guide siRNA does not contribute to specificity of target recognition, while the penultimate nucleotide of the 3' overhang affects target RNA cleavage, and a mismatch reduces RNAi 2- to 4-fold. The 5' end of a guide siRNA also appears more permissive for mismatched target RNA recognition when compared to the 3' end. Nucleotides in the centre of the siRNA, located opposite the target RNA cleavage site, are important specificity determinants and even single nucleotide changes reduce RNAi to undetectable level. This suggests that siRNA duplexes may be able to discriminate mutant or polymorphic alleles in gene targeting experiments, which may become an important feature for future therapeutic developments.

Similarly, Elbashir et al have taught position effects of mismatches in siRNA function. At page 6878 it is taught, for example that target recognition is extremely specific, as even single nucleotide mismatches between the siRNA duplex and the target mRNA abolish interference. And assert that this provide a rational basis for the design of siRNAs. At page 6885 it has been taught that "[n]ucleotides in the center of the siRNA, located opposite to the target RNA cleavage site, are important specificity determinants and even single nucleotide changes reduce RNAi to undetectable levels. This suggests that siRNA duplexes may be able to discriminate mutant or polymorphic alleles in gene targeting experiments, which may become an important feature for future therapeutic developments."

Both Tuschl et al and Elbashir have therefore taught that siRNA discriminate and inhibit targets with as little as one nucleotide change and have also taught where in the siRNA molecule such changes can be made with the most effective selection of target.

Tuschl et al and Elbashir do not specifically teach targeting gain of function alleles but certainly teach targeting mutant and polymorphic alleles which does embrace dominant gain of function mutations.

Brown et al have taught the involvement of SOD1 and in particular specific mutations in SOD1 that lead to dominant gain of function ALS (see page 28, for example). At pages 10, 31, 53, and claims 43-45 and 47, for example) it is taught to inhibit mutant SOD1 via antisense. In Tables 3A and 3C, the specific mutations targeted by the instant invention are disclosed [G256C and G281C which correspond to G85Arg and G93A].

Klug et al have taught the targeting of the most common SOD1 mutant gain of function allele G93A with antisense. It was shown the selective inhibition of the mutant allele and uptake of antisense in the brain.

Siddique et al have disclosed SOD1 mutations associated with ALS (see Table, for example).

Kunst et al have also shown that the specific mutant alleles for SOD1 associated ALS were well known at the time of invention (see Figure 1, for example.

The prior art has therefore shown that SOD1 dominant gain of function mutants are causative for ALS. The prior art has shown the targeted inhibition of specific SOD1 alleles via antisense.

The prior art has taught that siRNA can be used to specifically target a desired allele of a gene and that siRNA compounds are more effective inhibitors than antisence [prior art compound of the same class, for example]. The prior art has also taught to specifically inhibit dominant gain of function alleles, including the specific allele of SOD1 recited in the instant claims.

The prior art has shown that mutations associated with ALS (SOD1) have been known for some time before the instant invention. The prior art has also taught to target the mutant alleles of SOD1 selectively over the wt. Since the prior art has also asserted the usefulness of siRNA for treating disease it would have been obvious to use them since the prior art has shown that such targeting was successful using antisense. Since the sequence of SOD1 and more importantly since the specific mutant sequences were

known and the art clearly suggest targeting them, the siRNA sequences of the instant invention are merely optimizations at best.

The invention as a whole would therefore have been *prima facie* obvious at the time the invention was made.

Claims 41-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tuschl et al [US 20042059247 A1], Elbashir [The EMBO Journal Vol. 20(23), 2001, cited by applicant as C15 in IDS filed 9/17/07], Klug et al [European Journal of Physiology, Vol. 441 (6 Suppl): R205, 2001], Brown et al [WO 94/19493], Siddique et al [Neurology Vol. 47(suppl 2): S27-S35, 1996], and Kunst et al [Nature Genetics Vol. 15: 91-94, 01/15/96]. as applied to claims 1-12 and 28-40 above, and further in view of Brummelkamp et al [Science Express, 21 March 2002, cited by applicant as C6 on IDS filed 9/17/07.

The added limitations addressed herein are the expression of siRNAs of the invention from a vector and such that the siRNA are first expressed as an shRNA and the use of recited Pol III promoter.

Brummelkamp et al have taught the use of pSuper vectors that utilize pol III promoter to express siRNA as shRNA for the benefit of stable expression of siRNA to mediate persistent suppression of a target gene allowing for the analysis of loss of function phenotypes that developed over an extended period of time. One in the art

would clearly have recognized this extended expression benefit in the treatment of disease since one in the art would clearly recognize that the successful treatment of a genetic disease would benefit from administration of a drug that is stably expressed that over that of transient administration, for example. The prior art has taught the use of Pol III promoters such as the recited U6 promoter has been widely used, as the HI exemplified in Brummelkamp. Those in the art are well aware of the benefits of using Pol III promoters to express short RNAs.

The invention as a whole would therefore have been *prima facie* obvious to one in the art at the time the invention was made.

Claim Objections

Claim 5 **was** objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. This objection has been withdrawn in view of applicants arguments filed 7/11/08.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sean R. McGarry whose telephone number is (571) 272-0761. The examiner can normally be reached on M-Th (6:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz can be reached on (571) 272-0763. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Sean R McGarry
Primary Examiner
Art Unit 1635

/Sean R McGarry/
Primary Examiner, Art Unit 1635